REMARKS/ARGUMENTS

Claims 1-5 and 7-9 are pending.

Claims 6 and 8-29 have been cancelled.

Support for the amendments is found in the claims and specification, as originally filed. No new matter is believed to have been added.

Applicants wish to thank the Examiner for indicating allowable subject matter of claims 4 and 5.

The objection to Claim 9 and the rejections of Claims 8-9 under 35 U.S.C. 112, first paragraph, for lack of written description and 112, second paragraph, are not applicable to the claims presented herein as claims 8-9 have been cancelled. Applicants request that the objection and the rejections be withdrawn.

Claims 1-3 and 7 are rejected 35 U.S.C. 103(a) over Schirle et al., J. Immun. Methods, 257:1-16 (2001), Powell et al., US 2007/0031882, Tatsumi et al., Can. Res., 63:4481-4489 (8/2003), and Parker et al., J. Immunol., 152:163 (1994). Applicants traverse.

Tatsumi et al. is published on August 1, 2003. The present application is a national stage of the PCT/FR03/01280 application filed on April 23, 2003, claiming priority to the FR 02/05048 application filed on April 23, 2002. Also, the present application is an English translation the PCT/FR03/01280 application. Applicants request granting the claimed priority.

Concerning Schirle et al., Powell et al., and Parker et al., the skilled artisan would not have been motivated to obtain immunogenic T epitopes from the EphA2 protein by combining these references.

Powell et al. propose using antibodies against the EphA2 protein for modulating the protein activity in HIV infected T cells. As disclosed in paragraph [0276], page 41, these antibodies can be prepared by immunizing a suitable subject (e.g., rabbit, goat, mouse or other mammals) using standard techniques. Human EphA2 is xenogeneic "non-self" for rabbit, goat and mouse and generation of a humoral or cellular immune response against xenogeneic "non-self" proteins is very common. Since human EphA2 is an autologous self protein, it will be very unlikely that this protein generates a humoral and cellular immune response in human. Moreover, antibodies generated in animals are directed against B-epitopes recognized by the cognate animal immune system but not by the human immune system. The skilled artisan knows that the presence in a human protein of B-epitopes recognized by the animal immune system does not mean that said protein should have B-epitopes and more improbably T-epitopes recognized by the human immune system.

Schirle et al. teach prediction algorithms for the proteasomal cleavage. In the introduction section, Schirle et al. explain that the discovery in the 1990's of a peptide motif for every MHC-molecule was the first step for the development of the reverse immunology approach which Schirle et al. describe as the most successful strategy for T cell epitopes identification.

As stated on page 2, right column, last two sentences of the first paragraph, the reverse immunology approach shows a "high failure rate" due namely to identification of peptides not produced by the proteasome. Schirle et al. introduce prediction algorithms for the proteasomal cleavage in addition to reverse immunology in order to obtain more relevant results. Nevertheless, only 2 (second and third peptides of the table) over the 4 peptides presented table 1 page 4 are T epitopes predicted to be produced by the proteasome using PAPROC.

Moreover, Schirle et al. refer to an article by Kessler et al. (J. Exp. Med. 193:73-88, 2001, previously submitted), which disclose a study on the PRAME antigen (page 7, column 1, last paragraph). Only 4 out of the 19 high affinity binders peptides were found to be T epitopes. The inventors tested these 4 epitopes using PAPROC and FRAGPREDICT algorithms and considered prediction of the proteasomal cleavage when both algorithms gave a positive result simultaneously. None of these 4 epitopes was predicted by both algorithms in these conditions (*see* Declaration of Dr. Kosmatopoulos dated February 8, 2008 submitted with this paper).

These results on PRAME peptides also show that high affinity of a peptide for a HLA molecule is not sufficient for this peptide to be an epitope. A peptide must be produced by the proteasome digestion of the protein from which it is derived (see Declaration dated 12/05/2006, previously submitted). Kessler et al. also report that only 21% of high affinity HLA molecule binding peptides were found to be efficiently generated by the proteasome and presented by the HLA molecule.

Parker et al. teach the BIMAS program for finding high HLA affinity peptides but do not provide any information as to how to determine if a high HLA affinity peptide is an epitope.

The inventors have also tested the claimed immunogenic peptides (see Claim 2) in PAPROC and FRAGPREDICT algorithms and found that only two of them (SEQ ID NO: 6 and SEQ ID NO:8) were predicted to be epitopes, although these peptides are all naturally produced by the proteasome (*see* Declaration of Dr. Kosmatopoulos submitted with this paper).

Predictive models of the proteasome cleavage are also used in one of Dr. Kosmatopoulos' publications (Vaccine, 24:2102, 2006, submitted with this paper), which deals with a polypeptide vaccine composed of three different peptides. This work teaches

that only one out of six combinations of the 3 peptides described allows for the cleavage of all three peptides and elicits a trispecific immune response. The inventors have found that the predictive models, PAPROC and Netchop, were unable to predict the real sites of cleavage (page 2105, left column, 3.2) within the polypeptide and failed to identify the optimal polypeptide candidate. This recent publication shows that prediction algorithms for proteasomal cleavage are still irrelevant to identify immunogenic T epitopes.

Reading the article by Parker et al., the skilled artisan could apply the BIMAS program to the EphA2 protein only to identify high HLA affinity peptides. But the skilled artisan would not have been motivated by the Schirle proteasomal cleavage algorithms, nor by the Powell B-epitopes, to determine if the EphA2 contains T-epitopes. No information is given in Parker et al. about how to identify a T-epitope produced by the proteasome cleavage from a pool of high affinity peptides. Also, the skilled artisan would not have expected success by using prediction algorithms for the proteasomal cleavage taught by Schirle et al.

Thus, it would not have been obvious for one of ordinary skill in immunology at the time the claimed invention was made, to obtain EphA2 immunogenic T-cell peptides, on the basis of the disclosures of Schirle et al., Powell et al., and Parker et al.

Applicants request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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